Intravenous Immunoglobulin in Neonatal Sepsis

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Abstract

Neonatal sepsis remains the major cause of mortality and morbidity including neurodevelopmental impairment and prolonged hospital stay in newborn infants. Despite of advances in technology and optimal antibiotic treatment, incidence of neonatal sepsis and its complications remains unacceptably high especially in developing countries. Premature neonates in particular are at higher risk due to developmentally immature host defense mechanisms. Though not approved by Food and Drug Administration (FDA) U.S.A, off label use of intravenous immunoglobulin continues in many countries. Recent evidences showed no significant decrease in the mortality rate or other outcomes when intravenous immunoglobulin is administered in addition to standard therapies. Hence, use of intravenous immunoglobulin in suspected or proven neonatal sepsis is not recommended. The expense of prophylactic use of intravenous immunoglobulin administration for both term and preterm newborn population, given the minimal benefit is not justified. Future studies are required which should focus on other prophylactic or adjuvant treatment modalities in addition to the standard therapy in neonatal sepsis.

Introduction

Neonatal sepsis is a clinical syndrome characterized by systemic signs of infection and accompanied by bacteremia in the first month of life[1]. Sepsis occurring in the first 72 hours of life is defined as early-onset sepsis (EOS) and that occurring beyond 72 hours as late-onset sepsis (LOS)[2]. Neonatal early onset sepsis is defined by Centers for Disease Control and prevention (CDC) as blood or cerebrospinal fluid culture proven infection occurring in the newborn younger than 7 days of age. Neonatal late onset sepsis is usually defined as a culture-proven systemic infection in an infant between seven days and three months of age. For hospitalized VLBW infant, EOS is defined as culture-proven infection occurring at fewer than 72 hours of age[3]. Incidence of neonatal sepsis varies from 2.2/1000 live births in developed countries to 10-50/1000 live births in developing countries; though under reporting is common in both[4]. In China the incidence of neonatal sepsis accounts for 1%-10% of all neonates requiring medical attention and 13%-50% of all neonatal mortality cause[5]. The incidence of neonatal sepsis in India according to National Neonatal Perinatal Database is 30/1000 live births. Sepsis has been reported as cause of neonatal death in 20-50% cases in community based studies[6]. There is no national database mentioning incidence of neonatal sepsis in Nepal till date. Deaths occurring in the neonatal period each year account for 41% (3.6 million) of all deaths in children under five years of age[7,8]. In Nepal, out of the total infant mortality rate of 46/1000 live births, more than two-third, i.e. 33/1000 live births is contributed by neonatal mortality. Both the incidence of sepsis, 1/230 live births versus 1-5/1000 live term births and mortality from sepsis between 18-20% remain unacceptably high in VLBW preterm infants[9,10].

Neonates are comparatively immunocompromised in view of quantitative and qualitative deficiency in their humoral immunity. In addition, very preterm infants have reduced complement factors, opsonic activity, and polymorphonuclear chemotaxis and are liable to exhaust their storage pools[10,11].

Intravenous immunoglobulin

It has been more than 60 years since Ogden C. Bruton's reported use of human- plasma-derived IgG of an 8-year-old boy with agammaglobulinemia. IVIg has now become an important treatment option in a number of clinical indications beyond primary immunodeficiency,

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including autoimmune and acute inflammatory conditions[12]. Off-label prescribing has crossed over into almost every medical specialty including neonates.

Endogenous immunoglobulin synthesis does not begin until 24 weeks of life; young infants rely on in-utero maternally acquired immunoglobulins for protection against systemic infection. The placental transfer of these protective antibodies, however, does not occur until week 32 of gestation and post-natally IgG levels decrease due to reduced production in newborns. The administration of intravenous immunoglobulin (IVIg) may improve immune function by providing IgG that can bind to cell surface receptors, provide opsonic activity, activate complement, promote antibody dependent cytotoxicity, and improve neutrophilic chemo luminescence. However, there remains an ongoing debate about the efficacy of IVIg in the treatment of neonatal sepsis[13].

IVIg prophylaxis and adjuvant therapy

The first four studies published in 1981,1986,1988 and 1989 showed an increased risk of death in septic neonates given antibiotics but not treated with IVIg, compared to children given antibiotics plus IVIg, signifying the importance of IVIg as useful adjunctive therapy. The prophylactic role of IVIg was first studied in 1986 and 1987, which showed a benefit from the use of IVIg to prevent proven bacterial sepsis[14].

Various small single center clinical trials in mainland China have shown beneficial effects of use of IVIg in suspected or proven neonatal sepsis, especially premature infants[15-17]. On the contrary few recent trials have shown no effect of IVIg in prevention and treatment of neonatal sepsis in premature infants[18,19]. The effectiveness of IVIg preparations in the prevention or treatment of neonatal sepsis remained uncertain, due in part to studies that included relatively small or heterogeneous populations. Internationally there have been various studies with contradictory results. In 1994 first large clinical trial was done. The National Institute of Child Health and Human Development Neonatal Research Network published the largest randomized clinical trial (n=2,416) assessing the role of IVIg in the reduction of premature neonatal sepsis. The prophylactic administration of IVIg in this study did not reduce the incidence of nosocomial infections, morbidity and mortality in premature infants[20].

In the past 10 years, many systematic reviews and clinical trial results were published. In 2004 a systematic review by Cochrane collaboration evaluated the relationship between IVIg therapy and all-cause mortality during hospitalization in premature and term infants. Combining the results of 7studies (n=262), treatment with IVIg in cases of culture-proven infection resulted in a reduction in all-cause mortality (RR 0.55; 95% CI 0.31, 0.98)[21]. The authors did not observe between-study heterogeneity; however, (especially in a setting when fewer than 20 studies are analyzed), and the studies were different in the variety of IVIg products, different dosing regimens, and patient populations. In 2006 a multicenter (20 sites), randomized, double blinded, placebo controlled study evaluated the safety and efficacy of 2 infusions (14 days apart, dose = 1000 mg/Kg) of an anti-staphylococcal IVIg (Altastaph) in VLBW infants. The product was determined to be safe among the intervention group (n=104); however, when compared to placebo (n=102) no change was observed in the cumulative incidence of invasive staphylococcal infections[22].

In 2007, another multicenter, randomized clinical study involving 95 sites in the US and Canada evaluated the effect of up to 4 infusions of INH-A21 (Veronate, dose = 750 mg/Kg dosed on days 1, 3, 8 and 15), an anti-staphylococcal IVIg (anti-clumping Factor A and anti-Ser-Asp dipeptide repeat G), on the prevention of Staphylococcal late-onset sepsis among 1,983 infants with birth weights <1,250 g who received at least one infusion of study drug or placebo (989 vs. 994, respectively). In this study, no difference was observed between treatment groups in frequency of Staphylococcus aureus infections, 5% for INH-A21 vs 6% for placebo[23]. Pagibaximab, an anti-staphylococcal monoclonal antibody (anti-lipoteichoic acid) administered in 3 doses (7 days apart, 60 to 90 mg/kg/dose), was evaluated in a randomized, placebo controlled phase II study in infants with birth weight <1,300 g (n= 88). A trend was observed in the reduction of Staphylococcal bloodstream infections; none of the subjects in the 90 mg/kg group had confirmed staphylococcal sepsis compared to 20% and 13% in the 60 mg/kg and placebo groups, respectively (P<0.11)[24].

In 2010, Khalid N.Haque did a pragmatic review of 14 studies published within 1970 to 2010. The primary and only outcome parameter measured for this study was the impact of immunoglobulin therapy on mortality from neonatal sepsis. Analysis of 14 studies revealed a reduction of 48% in all cause mortality associated with neonatal sepsis when IVIg was used as an adjunct to standard therapy (OR 0.52; 95% CI 0.40-0.67)[25]. In the same year, Cochrane updated its previous review of intravenous immune globulin for infection in neonates with suspected or subsequently proven infection. It included 10 trials of variable quality undertaken in eight countries[26]. Mortality was reduced among patients with clinically suspected infection in 7 trials involving 378 infants (relative risk, 0.58; 95% CI, 0.38 to 0.89) and among patients with subsequently proven infection in 7

trials involving 262 patients (relative risk, 0.55; 95% CI, 0.31 to 0.98). Because of concerns about study quality, there was still insufficient evidence to support the routine administration of IVIg to prevent mortality in infants with suspected or subsequently proved neonatal infection. A large study of the effectiveness of IVIg in neonates with suspected infection had recently been completed. Results of the International Neonatal Immunotherapy Study (INIS trial)[27], which enrolled 3,493 infants, were expected to establish the usefulness of IVIg for suspected infection in newborns.

Latest Clinical Evidence

In 2011, the outcome of multicenter clinical trial organized by International Neonatal Immunotherapy Study (INIS) Collaborative Group was published. The trial enrolled 3493 infants receiving antibiotics for suspected or proven serious infection in the multicenter clinical trial at 113 hospitals in nine countries and randomly assigned to receive two infusions of either polyvalent IgG immune globulin (at a dose of 500 mg per kilogram of body weight) or matching placebo 48 hours apart. The primary outcome was death or major disability at the age of 2 years. The multicenter trial by INIS collaborative group showed no significant between-group difference in the rates of the primary outcome, which occurred in 686 of 1759 infants (39.0%) who received intravenous immune globulin and in 677 of 1734 infants (39.0%) who received placebo (relative risk, 1.00; 95% confidence interval, 0.92 to 1.08). Similarly, there were no significant differences in the rates of secondary outcomes, including the incidence of subsequent sepsis episodes. In follow-up of 2-year-old infants, there were no significant differences in the rates of major or non major disability or of adverse events[27].

In 2012, systematic review with meta-analysis by Andréia C. B. F. Franco et.al evaluated seven RCTs for the mortality rate, including 3,756 patients. The global effect of this outcome showed no statistically significant difference between the groups[28].

Conclusion

The development of IVIg has been a great achievement in medical history. But its use should be clinical evidence based. Latest evidence showed no significant benefits of IVIg use in neonatal sepsis. For the developing countries like Nepal, where the constraint for use of IVIg is its cost and availability, this result should come as a relief. In addition, prevention of ineffective expensive treatment therapy can save millions of dollars. Studies on other adjuvant therapies such as colony stimulating factors, probiotics, glutamine supplementation and lactoferrin have been tested with mixed results. In future, further large randomized clinical trials should evaluate the effectiveness of other adjuvant or prophylactic therapies for suspected or proven neonatal sepsis which may result in significant decrease in neonatal mortality and morbidity.

References

1. Klein J O. Bacteriology of neonatal sepsis. *Pediatr Infect Dis J* 1990; 9(10):777-78.
2. Stoll BJ, Hansen NI, S´anchez PJ, Faix RG, Poindexter BB, VanMeurs KP et al. Early onset neonatal sepsis: the burden of group B streptococcal and E.coli disease continues. *Pediatrics* 2011;127(5):817–26.
3. Falciglia G, Hageman JR, Schreiber M and Alexander K. Antibiotic Therapy and Early Onset Sepsis. *Neoreviews* 2012;13(2): e86-89.
4. Haque KN. Forfar and Arneil's Textbook of Pediatrics.5th ed. New York, Churchill Livingstone; 1998:273-289.
5. Xiaoming C, Text Book of Pediatrics. 7th ed. People's Health Publications Beijing; 2008:342-349.
6. Report of the National Neonatal Perinatal Database. National Neonatology Forum, India; 2002:e01-20
7. Demographic and Health Survey 2011 Preliminary report. MOHP, Govt. of Nepal. http://www.measuredhs.com/pubs/pdf/FR257/FR257%5B13April2012%5D.pdf
8. UNICEF statistics Nepal; 2011. http://www.unicef.org/infobycountry/nepal_nepal_statistics.html.
9. Kim KS. Use of Intravenous Immunoglobulin in the treatment of Neonatal Sepsis. *Am J Dis Child* 1989; 143(11):1257-1258.
10. Ferrieri P. Neonatal susceptibility and immunity to major bacterial pathogens. *Rev Infect Dis* 1990; 12(Suppl 4):S394-400.
11. Ohlsson A, Lacy JB. Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants. *The Cochrane Database of Systematic Rev.* 2004; Issue 1 Art No:CD000361
12. Clinical guidelines for immunoglobulin use, Second edition Update, 2011. Department of Health UK 2011. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/153238/dh_131107.pdf.pdf.
13. Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. *Cochrane Database Syst Rev*. 2004; CD001239.
14. Fischer GW. Use of intravenous immune globulin in newborn infants. *Clin Exp Immunol.*1994;97(Suppl 1):73-77

15. Sheng WD. Efficacy of intravenous gamma globulin in neonatal sepsis. *Chinese Community Doctors J* 2012;14(17):173-73.

16. Sheng GJ. A clinical study of IVIg preventing the early newborn baby from infection. *J China Prac Med* 2009;4(36):26-27.

17. Ping LX. Efficacy of intravenous immune globulin treatment of low-birth-weight infants with severe infections. *Beijing Med J* 2012;34(7):626-26.

18. Fen JH, Yan WH, Lin Z, Tao M. Intravenous gamma globulin to prevent preterm children from infection. *Rational Drug Use In Clinical Practice* J 2012; 5(2B):30-31.

19. Yong Z, Yan WH, Lin Z. The clinical effects of intravenous immunoglobulin in treatment of very low birth weight infant. Maternal and Child Care Service Center of Changzhou. *J Med Innovation China* 2012;9(2):16-17.

20. Fanaroff AA, Korones SB, Wright LL, Wright EC, Poland RL, Bauer CB et al. A controlled trial of intravenous immune globulin to reduce nosocomial infections in very-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. *N Engl J Med*. 1994;330(16):1107-13. [PubMed: 8133853]

21. Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. *Cochrane Database Syst Rev.* 2004:CD001239. [PubMed: 14973965]

22. Benjamin DK, Schelonka R, White R, Holly HP Jr, Bifano E, Cummings J et al. A blinded, randomized, multicenter study of an intravenous Staphylococcus aureus immune globulin. *J Perinatol* 2006;26(5):290-95. [PubMed: 16598296].

23. DeJonge M, Burchfield D, Bloom B, Duenas M, Walker W, Polak M et al. Clinical trial of safety and efficacy of INH-A21 for the prevention of nosocomial staphylococcal bloodstream infection in premature infants. *J Pediatr* 2007;151(3):260-65. [PubMed: 17719934].

24. Weisman LE, Thackray HM, Steinhorn RH, Walshet WF, Lassiter HA, Dhanireddy R et.al. A Randomized Study of a Monoclonal Antibody (Pagibaximab) to Prevent Staphylococcal Sepsis *Pediatrics* 2011;128(2):271-78.

25. Haque KN. Use of Intravenous Immunoglobulin in the Treatment of Neonatal Sepsis: A Pragmatic Review and Analysis. *J Med Sci* 2010;3(3):160-67.

26. Ohlsson A, Lacy J. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. *Cochrane Database Syst Rev* 2010;(3):CD001239.

27. INIS Collaborative Group, Brocklehurst P, Farrell B, King A, Juszczak E, Darlow B, Haque K et.al. *N Engl J Med* 2011;365(13):1201-11.

28. Franco AC, Torrico AC, Moreira FT, Sa FP, D'Elia HV, Bernardo WM. Adjuvant use of intravenous immunoglobulin in the treatment of neonatal sepsis: a systematic review with a meta-analysis. *J Pediatr (Rio J)* 2012;88(5):377-83.